Iron

Moderator: Sigismond Lasocki, Elvira Bisbe

Friday, May 01, 2026

1. IRON AND THE HEART

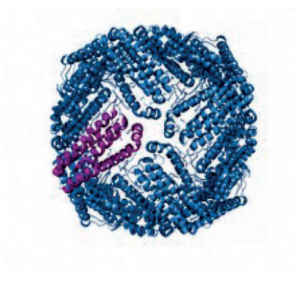
Mahir Karakas

Iron deficiency is a comorbidity in patients with heart failure (HF). The current guidelines of the *European Society of Cardiology* (ESC) recommend treatment with intravenous iron in symptomatic patients with HF and reduced or mildly reduced ejection fraction (< 50%) who have iron deficiency, with the aim of improving symptoms and quality of life and reducing the risk of hospitalization due to HF (evidences IA and IIA)[1].

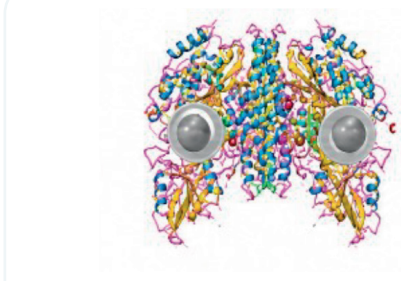
Iron deficiency has a "double effect": on the one hand, the reduction in haemoglobin compromises oxygen transport, on the other, it disrupts tissue utilisation of oxygen by reducing aerobic enzymes and diminishing oxygen utilisation and oxidative phosphorylation, thus reducing the generation of ATP, the energy molecule. This phenomenon is particularly relevant to the heart.

Consequently, iron deficiency is associated with a reduction in functional capacity, exercise intolerance and a decline in quality of life, even in the absence of overt anaemia.

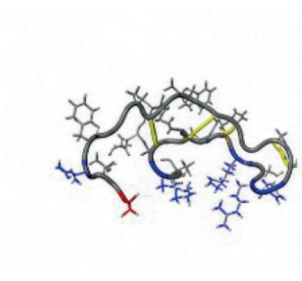
PARAMETERS FOR THE DEFINITION OF IRON DEFICIENCY IN CLINICAL TRIALS



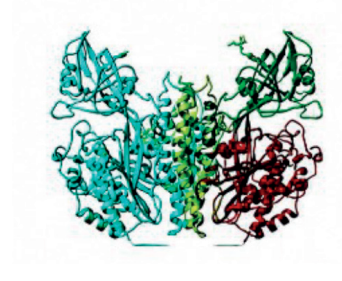
Ferritin



Transferrin saturation



Hepcidin



Soluble transferrin receptor

Definition of iron deficiency according to WHO in people over 4[2]:

- Serum ferritin < 15 µg/L in healthy subjects
- Ferritin < 70 µg/L if there is an infection or inflammation ➡ In this context, it must be taken into account that patients with heart failure usually present a state of subclinical chronic inflammation.

The classic definition of iron deficiency used in most HF trials has been the following[3-6]:

Ferritin ≤100 µg/L	**Ferritin 100–299 µg/L together with transferrin saturation (TSAT) <20%**

CLINICAL EVIDENCE DEVELOPMENT

The FAIR-HF study was the first clinical trial to demonstrate the efficacy of the intravenous administration of ferric carboxymaltose on the symptoms and quality of life in patients with HF and iron deficiency, regardless of the presence of anaemia[7]. In the subgroup of patients with baseline anaemia, the anaemia was resolved, while no significant changes were observed in non-anaemic patients.

Subsequently, the CONFIRM-HF study reported an improvement in functional capacity, as measured by the 6-minute walk test within 24 weeks after the intravenous administration of ferric carboxymaltose[8].

The AFFIRM-AHF study assessed the effect of intravenous ferric carboxymaltose in patients admitted for acute heart failure. A 21% decrease was observed in the combined rate of hospitalisations for HF and cardiovascular death versus placebo; however, this difference was not statistically significant[4]. The results were statistically significant in a secondary analysis that excluded the period following the outbreak of the COVID-19 pandemic, probably due to the loss of statistical power resulting from the interruption in follow-up visits.

A similar situation was observed in the IRONMAN trial, which assessed the efficacy of ferric derisomaltose. Although the overall analysis did not show a statistically significant reduction of hospitalizations due to HF and cardiovascular mortality, statistical significance was observed after excluding the period affected by the COVID-19 pandemic[3].

More recently, the HEART-FID trial assessed a hierarchical endpoint encompassing mortality, hospitalizations and functional capacity. Although a favourable trend was observed in all three variables, the differences were not statistical significance[5].

The FAIR-HF2 trial, the most recent to date, is a European, multicentre, double-blind, placebo-controlled study including over 1,100 patients. In this trial, ferric carboxymaltose was administered every four months until predefined safety criteria were met (Hb > 16 g/dL or ferritin > 800 µg/L). The study showed a non-significant 21% reduction in the combined endpoint of cardiovascular death or first hospitalization for HF. No significant reduction was either observed in the subgroup of patients with TSAT < 20%[6].

Finally, a meta-analysis including all six randomised clinical trials showed an overall 28% reduction in recurrent hospitalizations for HF and cardiovascular death at 12 months (RR 0.722; IC95 % 0.553–0.890). In the subgroup analysis, a significant interaction by sex was identified: the significant reduction in the risk of recurrent hospitalizations for HF and cardiovascular death associated with the administration of intravenous iron was significant in men, but not in women. In fact, the subgroups analyses in each individual trial have failed to demonstrate a consistent benefit in terms of prognostic endpoints in the female population.

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2. IRON AND REHABILITATION

Elvira Bisbe

WHY IS IRON IMPORTANT?

Beyond its effect on haemoglobin, iron deficiency has a direct impact on energy production in the skeletal muscle and causes metabolic abnormalities which ultimately lead to fatigue.

1) Reduction in glycogen stores

2) Increase in lactate production

3) Reduces Krebs cycle activity

4) Reduces beta oxidation

5) Accumulation of toxic intermediate lipids

6) Reduction in OXPHOS efficiency (electron transport chain)

7) Reduction in ATP levels in the muscle

8) Increase in lactate production

9) Accumulation of toxic intermediate lipids

It has recently been reported in animal models that iron deficiency reduces the proliferation of muscle stem cells and results in smaller regenerative fibres and poorer recovery of muscle mass, leading to sarcopenia[9].

EVIDENCE ON IRON DEFICIENCY AND REHABILITATION

In a prospective observational study of 140 patients with acute ischaemic stroke of the middle cerebral artery, the prevalence of iron deficiency was 48% at baseline and rose to 77% after one year of follow-up.

- Hand grip strength and quadriceps strength were lower in patients with iron deficiency compares to those with normal iron levels.
- Muscle strength only improved in patients with no iron deficiency.

EFFECT OF IRON DEFICIENCY TREATMENT IN REHABILITATION

In a meta-analysis including over 3000 patients with HF and iron deficiency, the use of intravenous iron was associated with a decrease in hospitalizations and readmissions for HF[10]. Furthermore, intravenous iron was linked to an improvement in exercise capacity, quality of life, overall assessment of patients and functional class (NYHA). Modest/neutral effect on mortality.

The IVICA multicentre trial included 116 patients with colorectal cancer and anaemia. Unlike oral administration, treatment with intravenous iron administered two weeks before surgery improved the following parameters[11]:

- Quality of life in the preoperative period (EQ-5D-5L) and up to 3 months after surgery.
- Each and every one of the 11 quality of life items assessed before surgery.
- Anaemia, fatigue and FACT-An score at 3 months.

In orthopaedic surgery, a randomised trial compared ferric carboxymaltose with oral iron for postoperative anaemia after total knee replacement. Patients treated with ferric carboxymaltose reached haemoglobin levels > 12 g/dL more frequently than those treated with oral iron. Likewise, subgroups with Hb < 10 g/dL and ferritin < 100 ng/mL, or both conditions, showed a faster recovery of haemoglobin. Moreover, patients treated with intravenous iron scored higher in the daily activities domain of EQ-5D[12]. One of the limitations of the trial was the use of the 6-minute walk test in patients who had undergone knee surgery.

In another prospective randomised study evaluating iron isomaltoside in patients with postoperative anaemia following total knee replacement, the treatment managed to reduce postoperative anaemia, although it did not improve functional recovery. The authors suggested that the administration of iron 3-4 weeks before surgery could be a decisive factor.

Taking into account these results and those obtained in the 2022 Cochrane meta-analysis on the effect of intravenous iron in patients with iron deficiency but without anaemia, it is possible that quality of life is not the most appropriate endpoint to prove the efficacy of intravenous iron in rehabilitation. In this context, variables such as fatigue, physical function or maximum oxygen uptake could be more sensitive targets[13].

TAKE HOME MESSAGES

- The use of iron should not be limited to correcting haemoglobin levels
- Iron is important not just in anaemic patients for rehabilitation
- Iron deficiency is consistently associated with fatigue and poorer functional recovery, as well as reduced skeletal muscle regeneration
- The evidence that the treatment with iron improves rehabilitation outcomes remains limited and depends on the context
- The challenge is not whether iron is important, but to identify who benefits, when, and how to measure its impact on rehabilitation.

In short, iron deficiency has a relevant impact on fatigue and functional recovery. However, the evidence supporting the use of intravenous iron in this context remains limited, and so it is fundamental to identify what patients can actually benefit from the treatment and what is the optimal time for its administration.

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3. IRON AND THE BONES PHYSIOLOGY

Heinz Zoller

The bone is a dynamic tissue that adapts to physical activity, but it also has biological memory. It has been shown that part of the benefits for bone size and strength associated with physical activity during youth can be maintained throughout life[14].

The bone regeneration process depends on the balance between osteoclast-mediated resorption and the synthesis of bone matrix by osteoblasts, followed by its mineralization[15]. Essential to this process is the formation of the collagen triple helix, mediated by prolyl-4-hydroxylase, an enzyme that depends on iron and ascorbic acid[16].

Recent data suggest an association between abnormalities in iron metabolism parameters, such as transferrin saturation and ferritin, and a higher risk of bone fracture[17]. However, iron deficiency is not yet included in traditional tools for calculating fracture risk, such as FRAXplus.

HYPOPHOSPHATEMIA INDUCED BY INTRAVENOUS IRON

Treatment with intravenous iron is associated with a higher risk of hypophosphatemia. In the PREVENTT study, for instance, the administration of ferric carboxymaltose to treat anaemia prior to major abdominal surgery brought about a significant reduction of preoperative serum phosphate levels, and approximately 10% of patients developed hypophosphatemia. This relatively low incidence is likely related to variability at the time of preoperative iron administration. In the same study, serum phosphate concentrations below 0.65 mM were associated with a longer average hospital stay[18].

Hypophosphatemia associated with intravenous iron varies in incidence and severity depending on the formulation used. It is also important to consider the duration of hypophosphatemia in each patient.

- The incidence of fractures is more than double in patients treated with ferric carboxymaltose compared with ferric derisomaltose, regardless of factors such as age, osteoporosis, anaemia, or calcium levels[19].
- The incidence of osteomalacia is higher with ferric carboxymaltose than with ferric derisomaltose in humans[19].

This could be explained by the pharmacokinetics of both drugs: ferric carboxymaltose tends to accumulate more (approximately as much) on the trabecular surface than ferric derisomaltose in mice[19]. Furthermore, it has been reported that in mice, collagen production is lower with a ferric carboxymaltose treatment than without treatment or with ferric derisomaltose[19].

As for the treatment of hypophosphatemia induced by the administration of intravenous iron, a recent study showed that oral phosphate supplementation does not prevent hypophosphatemia induced by ferric carboxymaltose[20].

IN SUMMARY, IT IS CRUCIAL TO BEAR IN MIND THE FOLLOWING ASPECTS[21]:

The incidence de hypophosphatemia associated with ferric carboxymaltose is high.	**Some symptoms of hypophosphatemia may be mistaken for those of iron deficiency (fatigue, asthenia, weakness or shortness of breath).**	**It is difficult to predict the severity of hypophosphatemia in each patient at any given time.**	**For the time being, there is no effective treatment.**

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CSL Behring